

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To

KOLSTER OY AB
Iso Roobertinkatu 23
P.O. Box 148
FIN-00121 Helsinki
FINLANDEDate of mailing (day-month-year)
04 April 2001 (04.04.01)Applicant's or agent's file reference
2980445PC/su

IMPORTANT NOTIFICATION

International application No.
PCT/FI99/00800International filing date (day-month-year)
29 September 1999 (29.09.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

VALIO LTD
Meijeritie 4
FIN-00370 Helsinki
Finland

State of Nationality

FI

State of Residence

FI

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

VALIO LTD
Meijeritie 6
FIN-00370 Helsinki
Finland

State of Nationality

FI

State of Residence

FI

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

A. Karkachi

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 June 2000 (08.06.00)	
International application No. PCT/FI99/00800	Applicant's or agent's file reference 2980445PC/su
International filing date (day/month/year) 29 September 1999 (29.09.99)	Priority date (day/month/year) 30 September 1998 (30.09.98)
Applicant VAARALA, Outi et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
25 April 2000 (25.04.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Manu Berrod Telephone No.: (41-22) 338.83.38
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FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

29 June 2001

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CLAIMS

1. A method of removing bovine insulin from a liquid fat-free proteinous material originating from cow's milk, **characterized** by

5 contacting the liquid fat-free proteinous material originating from cow's milk, the material having a pH of 2 to 8, at a temperature of less than 65°C, with an adsorption resin, whereby the weight ratio of the proteinous material to be treated to the adsorption resin is at most 100:1,

optionally combining with said resin treatment at least one ultra and dia-filtration treatment of the proteinous material, and

10 if necessary, concentrating the so obtained liquid material into a protein concentrate and optionally drying to powder.

2. A method as claimed in claim 1, **characterized** by using whey, a whey protein concentrate, skimmed milk or a casein solution, preferably whey, as the liquid fat-free proteinous material originating from cow's milk.

15 3. A method as claimed in claim 1 or 2, **characterized** by using a styrene-based or acrylic-based adsorption resin that is preferably microporous, as the adsorption resin.

4. A method as claimed in any one of claims 1 to 3, **characterized** in that the weight ratio of the proteinous material to be treated to the adsorption resin is suitably 10:1 to 40:1.

5. A method as claimed in any one of claims 1 to 4, **characterized** by introducing the proteinous material through a column, filled with an adsorption resin, at a flow rate of 1 to 20 column volumes (BV)/h, suitably 6 to 8 BV/h, at a temperature of 2 to 30°C, suitably 2 to 10°C.

25 6. A method as claimed in any one of claims 1 to 4, **characterized** by contacting the proteinous material with the adsorption resin at a temperature of 2 to 30°C, suitably 2 to 10°C, in a mixing vessel, whereby the contact time under mild mixing is below 2 hours, suitably 60 minutes.

7. A method as claimed in any one of claims 1 to 6, **characterized** by ultra and dia-filtering the liquid fat-free proteinous material originating from cow's milk using 5,000 to 25,000 D cut-off membranes, before bringing the proteinous material into contact with the adsorption resin and/or after the adsorption resin treatment.

35 8. A method as claimed in any one of claims 1 to 7, **characterized** by pretreating the liquid fat-free proteinous material originating

from cow's milk, before bringing it into contact with the adsorption resin, by clarifying it, suitably by microfiltration, ultrafiltration or centrifugation, preferably by filtering it through 0.05 to 1.4 micrometre microfiltration membranes, preferably 0.1 micrometre membranes.

5 9. A method as claimed in any one of claims 1 to 8, **characterized** by concentrating the liquid material, treated with the adsorption resin, by ultra and dia-filtration using 5,000 to 25,000 D cut-off membranes, suitably 10,000 D cut-off membranes, into a protein concentrate, which is optionally dried into a powder, suitably by spray or frost drying.

10 10. A substantially bovine insulin-free, fat-free proteinous material originating from cow's milk, **characterized** by being prepared by a method as claimed in any one of claims 1 to 9.

15 11. Use of a substantially bovine insulin-free, fat-free proteinous material, originating from cow's milk, and prepared by a method as claimed in any one of claims 1 to 9, as the protein part in infant formula or another special nutritive preparation or the raw material in consumption milk, other milk drinks or various milk preparations.

20 12. A method of preparing a substantially bovine insulin-free infant formula or other special nutritive preparation or consumption milk, other milk drink or other milk preparation or a raw material therefor, **characterized** by using a substantially bovine insulin-free, fat-free, proteinous material, originating from cow's milk, and prepared by a method as claimed in any one of claims 1 to 9 as the protein part in the preparation of a product.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 99/00800

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A23J 1/20, A23C 9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A23J, A23C, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9848640 A1 (VALIO LTD.), 5 November 1998 (05.11.98) --	1-12
Y	Dialog Information Services, File 155, MEDLINE, Dialog accession no.09430412, MEDLINE accession no. 98156374, Vaarala O.et al: "Cow milk feeding induces antibodies to insulin in children--a link between cow milk and insulin-dependent diabetes mellitus?": Scand J Immunol (ENGLAND) Feb 1998, 47 (2) p131-5 --	1-12
Y	US 4976865 A (VICTOR SANCHEZ ET AL), 11 December 1990 (11.12.90) --	1-12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 Sept 1999

Date of mailing of the international search report

13 -01- 2000

Name and mailing address of the ISA:

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Authorized officer

Hampus Rystedt/MP
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 99/00800

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5663291 A (RAINER OBERMEIER ET AL), 2 Sept 1997 (02.09.97), column 6, line 6 - line 26 --	1-12
A	EP 0601802 A1 (VALIO LTD.), 15 June 1994 (15.06.94) -- -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/FI 99/00800

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9848640	A1	05/11/98	AU	7047698 A	24/11/98
				FI	971872 A	31/10/98

US	4976865	A	11/12/90	AT	42044 T	15/04/89
				AU	577915 B	06/10/88
				AU	5161285 A	10/07/86
				CA	1278529 A	02/01/91
				DK	2186 A	05/07/86
				DK	165391 B,C	23/11/92
				EP	0189611 A,B	06/08/86
				SE	0189611 T3	
				ES	550599 A	01/03/87
				FR	2575666 A,B	11/07/86
				IE	58725 B	03/11/93
				NO	855317 A	07/07/86
				NZ	214636 A	06/01/89

US	5663291	A	02/09/97	AT	166069 T	15/05/98
				AU	699817 B	17/12/98
				AU	1228895 A	31/08/95
				CA	2142780 A	19/08/95
				DE	4405179 A	24/08/95
				DE	59502138 D	00/00/00
				EP	0668292 A,B	23/08/95
				SE	0668292 T3	
				ES	2119241 T	01/10/98
				FI	950699 A	19/08/95
				HK	1010457 A	00/00/00
				IL	112680 D	00/00/00
				JP	7265092 A	17/10/95
				NO	950592 A	21/08/95
				SG	46683 A	20/02/98

EP	0601802	A1	15/06/94	FI	94089 B,C	13/04/95
				FI	925620 A	11/06/94
				NO	934032 A	13/06/94

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REC'D 24 JAN 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2980445PC/su	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FI99/00800	International filing date (day/month/year) 29.09.1999	Priority date (day/month/year) 30.09.1998
International Patent Classification (IPC) or national classification and IPC7 A 23 J 1/20, A 23 C 9/14		
Applicant Valio LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 25.04.2000	Date of completion of this report 17.01.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Hampus Rystedt/EÖ Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/FI99/00800

1. Basis of the report

1. With regard to the **elements** of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages 1-11 . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____
- ☒ the claims:
pages _____ . as originally filed
pages _____ . as amended (together with any statement) under article 19
pages _____ . filed with the demand
pages 12-13 . filed with the letter of 09.01.2001
- ☐ the drawings:
pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/FI99/00800

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-12</u>	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	<u>1-12</u>	NO
Industrial applicability (IA)	Claims	<u>1-12</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application relates to a method for removing bovine insulin from a cow's milk derivative by ultra- or dia-filtering the derivative and mixing it with an adsorption resin.

The following documents are considered relevant:

D1: Vaarala et al, Scand J Immunol, 1998, vol 47, no 2, pp 131-135.

D2: EP-A1-601802

The reason for removing insulin from the milk derivative is that bovine insulin may induce diabetes in infants. This is known through D1.

D2 describes a method for removing allergenic proteins from proteinaceous compositions, e.g. whey protein or casein solutions, through the use of proteolytic enzymes, adsorption resins and filtration (see page 2 line 55-page 3 line 52).

The method of D2 differs from the method according to the application in that it does not state that insulin is a peptide that need to be removed and in that it uses proteolytic enzymes to hydrolyze proteins prior to the filtration step.

It was not known, at the time of publication of D2, that bovine insulin in milk could lead to immunization against insulin. This was not disclosed until D1 was published in 1998. It is considered obvious for a person skilled in the art to apply the method of D2 for removal of insulin once it is known that bovine insulin in milk poses a health risk to infants. Also, the method of the application does not necessarily use proteolytic enzymes to degrade proteins prior to the filtration step. Indeed, it is mentioned on page 3 line 4 of the description that "the new method does not even

.../...

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/FI99/00800

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

require protein hydrolysis". The reason for using proteolytic enzymes in the prior art is to hydrolyze the large allergenic proteins so that they may be efficiently removed (D2 page 2 lines 29-31). Since insulin is a smaller peptide that may not have to be degraded in order to be removed, and since the hydrolyzation step produces unwanted embittering peptides, it is considered obvious to a person skilled in the art that the hydrolyzation step may be superfluous. Also, the use of proteolytic enzymes is not excluded in the present claims.

The solution to the problem disclosed in D1 is consequently suggested by D2 and it is not considered inventive to apply this knowledge in order to arrive at the method according to claims 1-9 and 12 (claims 2-9 being technical adaptations of the method for the specific use of removing insulin), the material according to claim 10 or the use according to claim 11.